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Remarks

Claims 1-25 are under examination, claims 26-28 having been withdrawn from consideration. Claims 1, 3, 14 and 16 have been amended herein. Claims 11-13 have been canceled herein without prejudice. Support for amending the claim 1 language "platelet or other cell activation" to "cell activation mediated by a thrombin receptor by inhibiting cleavage of the thrombin receptor on said cells" can be found at page 5, lines 2-6, page 11, lines 8-11, page 23, line 29 to page 24, line 5, page 24, line 18, to 26, line 30, Figures 4-6, and Example 2. Support for amending the claim 14 language "platelet aggregation" to "thrombin-induced platelet aggregation mediated by cleavage of a thrombin receptor on said platelets " can be found at page 5, lines 2-6, page 7, lines 15-17, page 11, lines 8-10, and Examples 1 and 2. Support for amending claims 3 and 16 to recite "fragment of SEQ ID NO:1" can be found in the specification at page 9, lines 4-12, page 13, lines 8-17, page 20, line 26-28, page 21, lines 17-19, and page 23, lines 23-25.

Response to 35 U.S.C. § 112, second paragraph, rejection

Claims 1-25 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. The Examiner asserts that the term "other cell activation" in claim 1 is indefinite because it is unclear what activations would qualify as "other cell activation" within the meaning of the claim. The Examiner asserts that it is unclear if cell activation can be defined as any response to stimuli or just thrombin-induced stimuli and that one of ordinary skill cannot interpret the metes and bounds of the claim.

Although not necessarily agreeing with the assertion of the Examiner that the term "other cell activation" is indefinite with regard to "thrombin-induced platelet or other cell activation", claim 1 has been amended to expedite prosecution of the application. The phrase "platelet or other cell activation" of claim 1 has been amended to "cell activation mediated by cleavage of a thrombin receptor on said cells". Thrombin-induced activation of platelets and various cells, such as endothelial cells, brain cells, fibroblasts, smooth muscle cells, or other cells expressing the thrombin receptor, is supported throughout the specification as filed. For example, page 5, lines 4-6 refers to a compound of the invention as one "which inhibits thrombin activation of platelets or other cells which express the thrombin receptor" (see also page 11, lines 8-11 and 26-30 and Figs. 1-6). In addition,

compounds of the invention inhibit activation by "blocking cleavage of the thrombin receptor" (page 11, lines 23-25; see Examples at page 24, line 18 to page 26, line 29).

Therefore, Applicants submit that amended claim 1 and its dependent claims (2-10) are definite and that one of ordinary skill in the art would understand that the phrase "thrombin-induced cell activation mediated by cleavage of a thrombin receptor on said cells" encompasses thrombin-induced activation (stimulus) of cells, not activation by any stimulus.

The Examiner also alleges that recitation in claims 3 and 16 of X_1 being "from zero to thirty amino acids from amino acids 1-30 of SEQ ID NO:1" is indefinite. The Examiner asserts that it is unclear whether the zero to thirty amino acids are inclusive of specific fragments or are any amino acids from SEQ ID NO:1.

Although not necessarily agreeing with the reasoning of the Examiner, Applicants have amended claims 3 and 16 to recite that X_1 is "zero amino acids, SEQ ID NO:1, or a fragment of SEQ ID NO:1". Support for this amendment can be found at page 13, lines 8-17 of the specification where various fragments of the amino terminal portion (amino acids 1-30) of SEQ ID NO:1 are described. For example, a 30 amino acid fragment consisting of amino acids 1-30 of SEQ ID NO:1 and a 7 amino acid fragment consisting of amino acids 24-30 of SEQ ID NO:1 are described.

Therefore, Applicants submit that amended claims 3 and 16 are definite and that one of ordinary skill in the art would understand that the phrase "fragment of SEQ ID NO:1" encompasses specific fragments of SEQ ID NO:1, not random arrangements of the amino acids of SEQ ID NO:1.

The Examiner further alleges it is unclear how "segments" can be "different" in claims 5 and 18. The Examiner asserts that X_1 and X_2 are specifically defined in base claims and are required to be the same in the branched peptides.

Applicants respectfully submit that the Examiner has misinterpreted claims 5 and 18 with respect to "segments are different". Independent claims 1 and 14 each recite that a compound comprises one or more segments, and the segments are defined as having the amino acid sequence X_1-Arg-Pro-Pro-X_2. Thus, "segment" means X_1-Arg-Pro-Pro-X_2. Claims 1 and 14 each further recite that X_1 "may be the same or different" in "each segment" and that X_2 "may be the same or different" in "each segment". The term "each segment" refers to a compound where there is more than one segment, i.e., the compound is a

multimer of X_1-Arg-Pro-Pro-X_2 segments. Therefore, use of the term "segments are different" in dependent claims 5 and 18 is not indefinite because when there is more than one segment, each segment may be different. Moreover, as defined in claims 1 and 14, when there is more than one segment in a compound, X_1 may be different in each segment and X_2 may be different in each segment.

For the reasons described above, withdrawal of the 35 U.S.C. § 112, second paragraph rejection is respectfully requested.

Response to 35 U.S.C. § 112, first paragraph, enablement rejection

Claims 1-25 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly being non-enabled. Claims 11-13 have been canceled herein, therefore the enablement rejection as to these claims is moot. The Examiner asserts that the specification is only enabling for the following five peptides: SEQ ID NO:6 (RPPAF); SEQ ID NO: 7 (RPPGF); RPP; RPP MAP-4; and the peptide RPP heterodimer. The Examiner alleges that the specification enables inhibiting thrombin-induced platelet aggregation with these peptides. However, the Examiner alleges that the claims are not enabled for all of the claimed compounds and inhibition of "other cell activation."

A specification which discloses how to make and use a claimed invention is presumed to comply with the first paragraph of 35 U.S.C. § 112, unless there is a reason to doubt the objective truth of the specification. *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). Here, the present specification clearly discloses how to make and use the recited compounds in vitro and in vivo, and the Examiner has failed to rebut the assertions made therein.

The test of enablement is whether one reasonably skilled in the art could make or use the claimed invention from the teachings of the specification, coupled with information known in the art, without undue experimentation. *See* M.P.E.P. § 2164.01. The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* In the "unpredictable" arts such as chemistry and biotechnology, some experimentation may be required to identify compounds and methods which fall within the scope of the claims. However, as long as the experimentation does not "require ingenuity beyond that to be expected of one of ordinary skill in the art," the

experimentation will not be undue. *In re Angstadt*, 190 U.S.P.Q 214, 218 (CCPA 1976), citing *Fields v. Conover*, 170 U.S.P.Q 276, 279 (1971). For example, following specific directions provided in the specification (*e.g.*, detailed working examples) generally does not constitute "undue experimentation." See *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) and M.P.E.P. § 2164.06(b).

Here, one of ordinary skill in the art would have believed from the teachings of the specification and from their general knowledge, that additional compounds could be prepared and tested for the desired biological activity and could be used in methods of inhibiting thrombin-induced cell activation or thrombin-induced platelet aggregation.

The Examiner agrees that the art has recognized that peptides comprising the amino acids sequences of the five analogs described above inhibit thrombin-induced platelet activation and cell activation. The Examiner alleges that the art has also recognized that peptides comprising bradykinin fragments or analogs thereof, are not effective in inhibiting ADP-induced platelet activation, collagen activation, and U46619 cell activation, citing applicant's work (abstract, Hasan et al.). The Examiner states that Hasan et al. concludes that bradykinin analogs comprising the sequence RPPGF (Arg-Pro-Pro-Gly-Phe) are selective inhibitors of platelet activation. Applicants note that Examiner did not provide a specific citation for Hasan et al. and that three different Hasan et al. publications are cited in the IDS. However, Examiner appears to be referring to Hasan et al., 1996, Circulation, 94:517-528, based on the quotation by the Examiner. All references by Applicants to Hasan et al. are therefore to the 1996 Circulation publication.

Canceled claims 11-13 were the only claims which recited a method for inhibiting "ADP-induced" activation with compounds of the invention. Claim 1 as amended recites thrombin-induced activation, not ADP-induced activation. Independent claim 14 has also been amended to recite "a method for preventing thrombin-induced platelet aggregation mediated by cleavage of a thrombin receptor on said platelets". Because the claims now specifically recite "thrombin-induced" cell activation (claims 1-10) or "thrombin-induced" platelet aggregation (claim 14-23), the teachings of Hasan et al. regarding analogs of bradykinin as not inhibiting ADP-induced activation do not apply to the claimed invention. Applicants also note that the RPPGF sequence disclosed by Hasan is not applicable to the claimed invention, because a glycine cannot be the N-terminal amino acid of X_2. Therefore,

none of the assertions by the Examiner regarding ADP-induced activation or the RPPGF sequence are applicable to the invention as now claimed.

The teachings of Hasan et al. actually support that one of ordinary skill in the art at the time the application was filed was able to routinely prepare and screen bradykinin analogs for a desired biological activity. For example, in Hasan et al. twenty different synthetic peptides as large as 27 amino acids in length were prepared and subjected to numerous biological assays routinely performed by those of ordinary skill in the art to determine which peptides were selective inhibitors of α-thrombin-induced platelet activation. The peptides of Hasan were used in platelet aggregation studies, binding experiments, Ca^{2+} mobilization studies, and in various α-thrombin function studies. In addition, high molecular weight kininogen (64 amino acids in length) was tested in these assays.

The Examiner asserts that it is known in the art that the "three-dimensional structure of the peptide cannot be based on [primary] structure alone" and that it is not possible to simulate the folding process because contemporary hardware cannot perform the task (Ngo et al., "Computational Complexity, Protein Structure Prediction, and the Levinthal Paradox," The Protein Folding Problem and Tertiary Structure Prediction, pp. 491-494, 1994).

Ngo merely discusses complex mathematical methods to predict folding of proteins. Ngo does not assert that preparing peptides and testing their biological activity is not routine in the art.

The Examiner also cites Rudinger to support the assertion that one cannot a priori predict the role of particular amino acids or sequences in biological activity and that the role must be determined by experimental study ("Characteristics of the amino acids as components of a peptide hormone sequence," pages 1-7, in Peptide Hormones, ed. J. Parsons, 1976, University Park Press, Baltimore).

The Examiner has mistakenly equated Rudinger's use of the term "painstaking experimentation" with "undue experimentation." "Painstaking," merely means "careful or diligent" or "attentive to detail" (Webster's II New Collegiate Dictionary, copy enclosed). "Careful experimentation" or "diligent experimentation" is not synonymous with "undue experimentation". In addition, immediately following Rudinger's statement regarding experimentation, he states that careful design of analogs and screening them for biological

activity is the best way to determine biological activity of a peptide (Rudinger, page 6). Therefore, Hasan et al., Ngo et al., and Rudinger et al. do not support Examiner's assertion regarding the state of the art. In fact, these references indicate that it was routine to prepare and test peptides for biological activity.

The Examiner alleges that the unpredictably of the peptide art is very high, citing Rudinger et al.: "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the [sic] case to case by painstaking experimental study" (Rudinger, page 6).

Rudinger does not support the allegation that the art is unpredictable. Rudinger in fact demonstrates that at the time the application was filed, it was routine for one of ordinary skill in the art to prepare and test compounds comprising peptides of various sequences having a desired biological function. Similarly, Hasan et al. showed that it was routine to prepare and test numerous bradykinin analogs. Thus, at the time the specification was filed, one of ordinary skill in the art routinely prepared and screened potential amino acid sequences of peptide candidates for those peptides having a desired biological function.

The Examiner alleges that the breadth of the claims allows for any substitution up to 30 amino acids at the N-terminus and C-terminus of the RPP sequence, and that the claims provide that these sequences are all effective in inhibiting ADP-induced platelet aggregation, ADP-induced platelet activation and other cell activation.

As amended, the claims encompass methods of inhibiting "thrombin-induced" cell activation or platelet aggregation, not "other cell activation" or ADP-induced activation with compounds of the formulae recited in the claims. Therefore, Examiner's assertions as to ADP-induced activation are inapplicable to the claims as amended. Furthermore, the specification not only describes methods for preparing and testing peptides of various sizes, the specific anti-thrombin peptides described above comprise lengths of 3, 5, 8, and 16 amino acids in size, including various branched peptides (see Examples). Additionally, much larger peptides were tested, such as high molecular weight kininogen. High molecular weight kininogen (SEQ ID NO:1) is 64 amino acids in length (bradykinin is amino acids 31-39) and has thrombin inhibiting activity. Therefore, it is known that peptides of at least 64 amino acids may have activity in inhibiting thrombin-induced cell activation. A compound comprising the formula X_1-Arg-Pro-Pro-X_2 and containing 30 amino acids for each of X_1

and X_2, is a 63 amino acid peptide, which is one amino acid shorter than high molecular weight kininogen. Based on the teachings of the specification and the knowledge available at the time the application was filed, one of ordinary skill in the art would have been able to synthesize compounds comprising the formula X_1-Arg-Pro-Pro-X_2, including preparing X_1 or X_2 with varied sequences. Thus, the specification supports the preparation and use of various size peptides, which have the desired biologic activity, i.e., inhibition of thrombin-induced cell activation.

The Examiner further asserts that the claims allow for branched peptides which have up to 20 similar or different branches.

The specification provides several examples of branched peptides comprising the base RPP sequence. For example, a heterodimer (the RPP heterodimer) and a 4-branched peptide (RPP MAP-4) were prepared and shown to inhibit thrombin-induced activation and calcium mobilization and to bind to the thrombin receptor cleavage site (see Examples 4-7, pages 31-34). The specification provides ample description for synthesizing a multi-branched peptide. For example, the RPP heterodimer was prepared by first adding a lysine (K) residue to an RPP, yielding the 4-mer RPPK (page 32, line 25 to page 33, line 6). Then, an aspartic acid (D) residue is attached to the lysine of the 4-mer, yielding the 5-mer, RPPKD. Another RPP is then attached to the aspartic acid residue of the 5-mer, yielding the RPP heterodimer:

Arg-Pro-Pro-Lys
|
Arg-Pro-Pro-Asp.

The synthesis of the 4-branched peptide, RPP MAP-4, is described at page 32, lines 3-24. Further methods for preparation of multimers is provided at page 13, line 18, to page 17, line 22. Therefore, the application provides multiple examples of branched peptides with the ability to inhibit thrombin-induced cell activation or thrombin-induced platelet aggregation. One of ordinary skill in the art could easily use the teachings of the specification to synthesize peptides with multiple branches as recited in the claims, including peptides with as many as 20 branches.

The Examiner cites Hasan et al. to support the allegation that the art recognizes that not all peptides containing the sequence RPP are effective in inhibiting platelet activation and that RPPG containing peptides did not inhibit ADP-induced platelet activation. The

Examiner asserts that, given the similarity of the claimed peptide X_1-Arg-Pro-Pro-X_2, wherein X_2 cannot contain a glycine residue in the N-terminal to the RPPG peptide disclosed by Hasan, it would be unpredictable to determine the ADP-induced activation inhibitory activity of any peptide having the sequence RPP.

As discussed above, the claims as amended are directed to a method of inhibiting thrombin-induced activation, not ADP-induced activation. Moreover, the peptide of Hasan, RPPG, is not encompassed by the claims. Therefore, Hasan's failure to inhibit to ADP-induced cell activation using the RPPG peptide is inapposite to the enablement of the presently claimed invention.

The Examiner further asserts that the specification does not provide guidance for peptides having up to 30 amino acids at the amino or carboxy termini and that the specification does not provide examples of peptides of five or six amino acids which are effective inhibitors.

The specification provides multiple examples of peptides with the ability to inhibit thrombin-induced activation and provides adequate guidance for preparing and testing additional compounds for use in inhibiting the claimed thrombin-induced activation. Moreover, the specification describes more than just the five bradykinin analogs which the Examiner lists. Two additional peptides were prepared and shown to have the ability to inhibit thrombin-induced activity, (D-Arg)-Pro-Pro and Arg-(D-Pro)-Pro (page 33, lines 26-29).

Many methods for synthesizing peptides of various sizes, including peptides with amino or carboxy termini of up to 30 amino acids, were known to those of ordinary skill in the art at the time the application was filed. The specification describes methods to synthesize linear peptides as well as branched peptides (page 13, line 18 to page 16, line 25; page 31, line 15 to page 33, line 5). As described above, the specification provides peptides of 3, 5, 8, and 16 amino acids which inhibit thrombin-induced activation of cells or platelet aggregation. Additionally, Hasan et al. prepared peptides comprising up to 27 amino acids with anti-thrombin activity.

In addition, no more than routine experimentation is needed to test compounds prepared as described in the specification. A series of binding and functional assays can be combined to measure peptide inhibition of thrombin-induced cell activation or platelet

aggregation. Methods for measuring platelet activation, such as platelet aggregation, hydroxytryptamine secretion, calcium mobilization, and thrombin-receptor cleavage are clearly described in the application (page 21, line 1 to page 26, line 30, Figs. 1-4). For example, Figs. 2 and 3 clearly show that RPP, RPP heterodimer, and RPP MAP-4 inhibit γ-thrombin induced platelet activation, as measured by a platelet aggregation assay.

The specification provides examples of peptide inhibition of thrombin-induced activation of multiple cell types, peptide/thrombin receptor binding, and cleavage of the thrombin receptor (see Figs. 4-6 and Examples 1 and 5-7). Thrombin-induced activation of cells such as fibroblasts and endothelial cells can be measured with various assays, including mitogenesis assays, calcium mobilization assays, and thrombin receptor cleavage assays (page 11, lines 8-11, page 23, line 20 to page 26, line 29, Figs. 5 and 6). In addition, the use of combinatorial libraries to prepare and test peptides is described at page 18, lines 8-30, page 27, and page 35. High molecular weight kininogen itself (64 amino acids) has amino and carboxy terminal peptides of 30 amino acids and 25 amino acids, respectively, adjacent to the bradykinin fragment. Hasan et al. has also tested synthetic peptide inhibitors of thrombin of up to 27 amino acids in length. One of ordinary skill in the art would therefore be able to follow the teachings of the specification and prepare and test peptides of various sizes according to the formulae of the invention, including peptides wherein X_1 or X_2 are up to 30 amino acids in length, and obtain peptides with the desired biological activity.

Therefore, the specification as filed provides sufficient guidance to allow one of ordinary skill in the art to make and use compounds for inhibiting thrombin-induced cell activation or thrombin-induced platelet aggregation, as recited in the claims.

Applicants request that the rejection under 35 U.S.C. § 112, first paragraph as to amended claims 1-10 and 14-25 (claims 11-13 having been canceled), be withdrawn.

Conclusion

Based on the foregoing, all claims are believed in condition for allowance. An early and favorable action toward that end is earnestly solicited.

Respectfully submitted,

ALVIN SCHMAIER et al.

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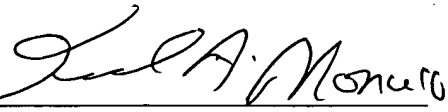
BY 

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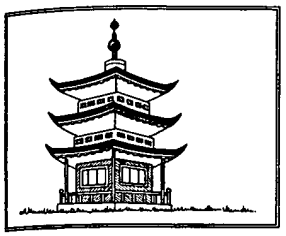
pag·i·na·tion (păj′ə-nā′shən) *n.* **1.** The system by which pages are numbered. **2.** The arrangement and number of pages in a book, as noted in a catalog or bibliography.

pag·ing (pā′jĭng) *n. Computer Sci.* The transfer of pages of data from a computer's main memory to an auxiliary memory.

pa·go·da (pə-gō′də) *n.* [Port. *pagode,* poss. of Dravidian orig.] **1.** A religious building of the Far East, esp. a many-storied Buddhist tower erected as a memorial or shrine. **2.** A pagodalike structure, as a garden pavilion.



pagoda

pah (pä) *interj.* —Used to express irritation or disgust.

pah·la·vi (pä′lə-vē′) *n., pl.* **-vis.** [Pers. *pahlawī,* after Mohammed Reza *Pahlavi* (1919–1980), Shah of Iran.] A gold coin once used in Iran.

Pah·la·vi (pä′lə-vē′) *also* **Peh·le·vi** (pā′lə-vē′) *n.* [Pers. *pahlawī* <*Pahlav,* Parthia.] An Iranian language used in Persia during the reign of the Sassanids.

paid[1] (pād) *v. p.t. & p.p. of* PAY[1].

paid[2] (pād) *v. var. p.t. & p.p. of* PAY[2].

pail (pāl) *n.* [ME *payle* < OE *pægel.*] **1.** A watertight cylindrical vessel, open at the top and fitted with a handle : BUCKET. **2.** The amount contained in a pail. **—pail′ful′** *adj.*

pail·lasse *also* **pal·liasse** (păl-yăs′, păl′yăs′) *n.* [Fr. < *paille,* straw < Lat. *palea.*] A thin mattress filled with sawdust or straw.

pail·lette (pā-yĕt′, pā-, pă-lĕt′) *n.* [Fr., dim. of *paille,* straw. —see PAILLASSE.] **1.** A small piece of metal or foil, used in enamel painting. **2.** A spangle used to decorate a dress or costume.

pain (pān) *n.* [ME < OFr. *peine* < Lat. *poena* < Gk. *poinē,* penalty.] **1.** An unpleasant sensation, occurring in varying degrees of severity as a consequence of injury, disease, or emotional disorder. **2.** Suffering or distress. **3. pains.** The pangs of childbirth. **4. pains.** Great care or effort <took *pains* to do it right> **5.** *Informal.* A nuisance. —*v.* **pained, pain·ing, pains.** —*vt.* To cause pain to : HURT. —*vi.* To be the cause of pain. **—on** (*or* **upon** *or* **under) pain of.** Subject to the penalty of a given punishment, as death. **—pain in the neck.** A source of annoyance.

pain·ful (pān′fəl) *adj.* **1.** Causing pain. **2.** Full of pain. **3.** Requiring care and labor : IRKSOME <a *painful* chore> **4.** *Archaic.* Diligent : careful. **—pain′ful·ly** *adv.* **—pain′ful·ness** *n.*

★ ***syns:*** PAINFUL, ACHING, AFFLICTIVE, HURTFUL, SMARTING, SORE *adj. core meaning* : marked by, causing, or experiencing physical pain <a *painful* back injury> ***ant:*** PAINLESS

pain·kill·er (pān′kĭl′ər) *n.* An agent, as a drug, that relieves pain. **—pain′kill′ing** *adj.*

pain·less (pān′lĭs) *adj.* Free from pain or complication <a *painless* surgical procedure> **—pain′less·ly** *adv.* **—pain′less·ness** *n.*

pain principle *n. Psychoanal.* The unconscious desire for pain or destruction.

pains·tak·ing (pānz′tā′kĭng) *adj.* Diligent and attentive to detail : CAREFUL. —*n.* Diligence and attentiveness. **—pains′tak′ing·ly** *adv.*

paint (pānt) *n.* [< ME *painten,* to paint < OFr. *peindre* < Lat. *pingere.*] **1.** a. A liquid mixture, usu. of a solid pigment in a liquid vehicle, used as a protective or decorative coating. **b.** The thin dry film formed by such a mixture applied to a surface. **c.** The solid pigment before it is mixed with a vehicle. **2.** A cosmetic, esp. one that colors, as rouge. **3.** A pinto. —*v.* **paint·ed, paint·ing, paints.** —*vt.* **1.** To make with paints <*paint* a picture> **2. a.** To represent in a picture with paints. **b.** To depict vividly in words. **3.** To coat or decorate with paint <*paint* a room> **4.** To apply cosmetics to. **5.** To apply medicine to : SWAB <*paint* a cut> —*vi.* **1.** To practice the art of painting pictures. **2.** To cover something with paint. **3.** To apply make-up. **4.** To serve as a surface to be coated with paint <a surface that *paints* well> **—paint the town red.** *Slang.* To go on a spree.

paint·brush (pānt′brŭsh′) *n.* A brush for applying paint.

paint·ed (pān′tĭd) *adj.* **1.** Represented in paint. **2. a.** Covered or decorated with paint. **b.** Brightly colored : GAUDY. **3.** Excessively made up with cosmetics. **4.** Having no reality : ARTIFICIAL.

painted bunting *n.* A small bird of the southern United States, *Passerina ciris,* with brilliant multicolored plumage.

painted cup *n.* The Indian paintbrush.

painted lady *n.* A widely distributed butterfly, *Vanessa cardui,* with brown, black, and orange markings.

paint·er[1] (pān′tər) *n.* One who paints, either as an artist or a worker.

pain·ter[2] (pān′tər) *n.* [ME *paynter,* poss. < OFr. *pentoir,* strong rope < *pendre,* to hand < Lat. *pendēre.*] *Naut.* A rope attached to the bow of a boat, used for tying up.

†pain·ter[3] (pān′tər) *n.* [Alteration of PANTHER.] *Regional.* A mountain lion or lynx.

paint·er·ly (pān′tər-lē) *adj.* **1.** Of, relating to, or typical of a painter : ARTISTIC. **2. a.** Having qualities unique to the art of painting. **b.** Designating a style of painting characterized by openness of form, with shapes distinguished by variations of color rather than by outline or contour. **—paint′er·li·ness** *n.*

painter's colic *n.* [So called because the disease is often caused by exposure to lead-base paint.] Chronic intestinal pains and constipation resulting usu. from lead poisoning.

paint·ing (pān′tĭng). **1.** The art, process, or occupation of coating surfaces with paint. **2.** A picture or design in paint.

pair (pâr) *n., pl.* **pair** *also* **pairs.** [ME < OFr. *paire* < Lat. *paria* < *par,* equal.] **1.** Two corresponding persons or items, similar in form or function and matched or associated. **2.** One object consisting of two joined, similar parts that are dependent on each other <a *pair* of scissors> **3. a.** Two persons joined together in marriage or engagement. **b.** Two persons having something in common and considered together <a *pair* of golfers> **c.** Two mated animals. **d.** Two animals joined together in work. **4.** Two playing cards of the same denomination. **5.** Two members of a deliberative body with opposing opinions on a given issue who offset each other by agreeing to abstain from voting on the issue. **6.** *Chem.* An electron pair. —*v.* **paired, pair·ing, pairs.** —*vt.* **1.** To arrange in sets of two : COUPLE. **2.** To join in a pair : MATE. **3.** To provide a partner for. —*vi.* **1.** To form a pair or pairs. **2.** To join as mates in marriage.

pair of compasses *n.* COMPASS 1c.

pair of virginals *n.* A virginal.

pair production *n.* The simultaneous creation of a positron and electron from a high-energy gamma ray in a very strong electric field, esp. in that of an atomic nucleus.

pai·sa (pī-sä′) *n., pl.* **pai·se** (pī-sā′) *or* **pai·sas.** [Hindi *paisā.*] —See table at CURRENCY.

pai·sa·no (pī-zä′nō) *also* **pai·san** (pī-zän′) *n., pl.* **-sa·nos** *also* **-sans.** [Sp. < Fr. *paysan* < OFr. *païsant,* peasant. —see PEASANT.] **1.** Countryman : compatriot. **2.** *Slang.* Friend : pal.

pais·ley (pāz′lē) *adj.* [After *Paisley,* Scotland.] **1.** Made of a soft wool fabric with a woven or printed colorful, swirled pattern of abstract, curved shapes, derived from the palmette motif of Persian rugs. **2.** Marked with a paisley pattern. —*n., pl.* **-leys.** An article of clothing, as a shawl, made of paisley.

Pai·ute *also* **Pi·ute** (pī′yōōt′) *n., pl.* **Paiute** *or* **-utes** *also* **Piute** *or* **-utes. 1. a.** Either of two distinct American Indian peoples, the Northern Paiute and the Southern Paiute, inhabiting parts of the Great Basin desert in Nevada, Utah, and adjacent areas of Oregon, California, and Arizona. **b.** A member of either of these peoples. **2.** The Shoshonean language of the Paiute. **—Pai′ute′** *adj.*

pa·ja·mas (pə-jä′məz, -jăm′əz) *pl.n.* [Hindi *pāejāma,* loose-fitting trousers : Pers. *pāī,* leg + Pers. *jāmah,* garment.] **1.** A loose-fitting garment consisting of trousers and a jacket, worn for sleeping or lounging. **2.** Loose-fitting trousers worn by both sexes in Asia.

pak choi (bäk′ choi′) *n.* [Chin. *bai*[2] *car*[4] : *bai*[2], white + *cai*[4], vegetable.] A Chinese plant, *Brassica chinensis,* similar to the common cabbage and used as a vegetable.

pal (păl) [Romany *phal, phrall* < Skt. *bhrātṛ,* brother.] *Informal.* —*n.* A friend : chum. —*vi.* **palled, pal·ling, pals.** To associate as pals <*palled* around together>

pal·ace (păl′ĭs) *n.* [ME < OFr. *palais* < Lat. *palatium* < *Palatium,* Palatine Hill, Rome, Italy (from its being the site where emperors built their homes).] **1.** The official residence of a royal person. **2.** *Chiefly Brit.* The official residence of a high-ranking dignitary, as a bishop or archbishop. **3. a.** A large or splendid residence. **b.** A large, often ornate building used for entertainment or exhibitions.

pal·a·din (păl′ə-dĭn) *n.* [Fr. < Ital. *paladino* < Lat. *palatinus,* palatine.] **1.** One of the 12 peers of Charlemagne's court. **2.** A heroic paragon of chivalry.

palaeo– *or* **palae–** *pref. vars. of* PALEO-.

pa·laes·tra (pə-lĕs′trə) *n. var. of* PALESTRA.

pal·an·quin *also* **pal·an·keen** (păl′ən-kēn′) *n.* [Port. *palanquin* < Javanese *pēlangki* < Skt. *palyankaḥ, paryankaḥ,* bed : *pari,* around + *añcati,* he bends.] An eastern Asian covered litter, carried on poles on the shoulders of two or four men.

pal·at·a·ble (păl′ə-tə-bəl) *adj.* [< PALATE.] **1.** Sufficiently agreeable in flavor to be eaten. **2.** Acceptable to the mind or sensibilities <a *palatable* resolution of the dispute> **—pal′at·a·bil′i·ty, pal′at·a·ble·ness** *n.* **—pal′at·a·bly** *adv.*

pal·a·tal (păl′ə-təl) *adj.* **1.** Of or pertaining to the palate. **2. a.** Produced with the front of the tongue near or against the hard palate, as the (y) in English *youth.* **b.** Produced with the blade of the tongue near the hard palate, as the (ch) in English *chair.* **c.** Produced with the front of the tongue in a forward position. —Used of a vowel. —*n.* A palatal sound. **—pal′a·tal·ly** *adv.*

) *adj.* 1. Not tending toward a state of rest oscillations. 2. Not diminished or discour-

n'tə-bəl, -dān'-) *adj.* Not capable of being ed.

(d, -dān'-) *adj.* Not discouraged : RESOLUTE. : —**un·daunt'ed·ness** *n.*

') *vt.* **-ceived, -ceiv·ing, -ceives.** To ision.

dĭd) *adj.* 1. Not yet settled or determined. cision. —**un'de·cid'ed·ly** *adv.* —**un'-**

ıdj. Not decorated or unornamented. *adj. Naut.* Having no deck. —Used of a

(ŭn'dĭ-mŏn'strə-tĭv) *adj.* Not given to ex- RVED. —**un'de·mon'stra·tive·ly** *adv.* 'e·ness *n.*

ıī'ə-bəl) *adj.* 1. Not able to be denied : IR- ably good <*undeniable* credit references> ə *n.* —**un'de·ni'a·bly** *adv.*

E < OE.] 1. In a lower position or place than 2. Beneath the surface of <*under* the snow> face or guise of <entered the country *under* n : smaller than. 5. Less than the required *der* drinking age> 6. Inferior to in rank or ithority, rule, or control of <*under* a tyran- the supervision, instruction, or influence of > 9. Undergoing or receiving the effects of . Subject to the restraint or obligation of <a studio> 11. Within the group or classifica- istry> 12. In the process of <a plan *under* f <*under* those conditions> 14. With the he monarch's seal> 15. Sowed or planted · —*adv.* 1. In or into a place below or be- rdinate or inferior condition or position. 3. veloped by. 4. So as to be less than the re- – *adj.* 1. Located or situated on a lower lev- ıe <the *under* parts of a machine> 2. Lower ty : SUBORDINATE. 3. Less than required or : of antibiotics>

: *under,* under.] 1. Beneath or below in po- Inferior or subordinate in rank or impor- 3. Less in degree, rate, or quantity than ized>

lar-ə-chēv') *vi.* **-chieved, -chiev·ing,** ɔrm at the level of capability indicated by ɔtitude, esp. in schoolwork. —**un'der·a· der·a·chiev'er** *n.*

v. **-act·ed, -act·ing, -acts.** —*vt.* 1. To To understate (a role) intentionally. —*vi.* ted way.

adj. Below the legal or customary age, as

ı') *adj.* 1. Located, placed, or used under the hand kept below the level of the shoul- —*adv.* With an underarm motion or de-

ël'ē) *n., pl.* **-lies.** 1. The lower part or un- . 2. The vulnerable or weak part <"the soft Winston Churchill>

v. **-bid, -bid·ding, -bids.** —*vt.* 1. To tor). 2. To bid less than the full value of *vi.* To bid unnecessarily low. —**un'der·**

ŏd'ē) *n.* 1. UNDERBELLY 1. 2. The under ır vehicle.

d') *adj.* 1. Badly brought up : ILL-BRED. 2.

ŭsh') *n.* Small trees, shrubs, or similar : taller trees in a forest.

ər-kär'ĭj) *n.* 1. The supporting framework g gear of an aircraft.

r-chärj') *vt.* **-charged, -charg·ing,** (someone) less than is customary or re- n) with an insufficient charge. —*n.* (ŭn'- or improper charge.

ls') *n.* The lowest stratum of society, usu. ıged.

'dər-klās'mən) *n.* A freshman or sopho- l or college.

-klōz', -klōthz') *pl.n.* Clothes worn next

ler-klō'*th*ĭng) *n.* Underclothes.

father ĕ pet ē be hw which ĭ pit
toe ô paw, for oi noise o͝o took

un·der·coat (ŭn'dər-kōt') *n.* 1. A coat worn beneath another coat. 2. A growth of short hairs or fur concealed by the longer outer hairs of an animal's coat. 3. *also* **un·der·coat·ing** (-kō'tĭng). a. A coat of sealing material applied to a surface as a base for the topcoat. b. A rubberlike substance applied to the underside of a motor vehicle to prevent rust. —*vt.* **-coat·ed, -coat·ing, -coats.** To apply an undercoat to <*undercoat* a new truck>

un·der·cool (ŭn'dər-kōol') *vt.* **-cooled, -cool·ing, -cools.** To supercool.

un·der·cov·er (ŭn'dər-kŭv'ər) *adj.* 1. Carried out in secret <an *undercover* investigation> 2. Engaged or employed in spying or secret investigation <an *undercover* agent>

un·der·croft (ŭn'dər-krôft', -krŏft') *n.* [ME *under croft* : *under,* under + *croft,* crypt < Med. Lat. *crupta* < Lat. *crypta.* —see CRYPT.] A crypt, esp. one under a church.

un·der·cur·rent (ŭn'dər-kûr'ənt) *n.* 1. A current, as of air or water, below another current or beneath a surface. 2. An underlying tendency or feeling often at odds with what is superficially evident : INTIMATION <an *undercurrent* of hostility>

un·der·cut (ŭn'dər-kŭt') *v.* **-cut, -cut·ting, -cuts.** —*vt.* 1. To make a cut under or below. 2. To create an overhang by cutting material away from, as in carving. 3. To sell at lower prices or work for lower wages than (a competitor). 4. To diminish or destroy the province or effectiveness of : UNDERMINE. 5. a. To impart backspin to (a ball) by striking downward as well as forward, as in golf and baseball. b. To cut or slice (a ball) with an underarm stroke, as in tennis. —*vi.* To undercut someone or something. —*n.* (ŭn'dər-kŭt'). 1. a. A cut made in the under part to remove material. b. The material so removed. 2. A notch cut in the base of a tree to direct its fall and insure a clean break. 3. *Chiefly Brit.* The tenderloin or fillet of beef. 4. a. A backspin given to a ball, as in golf. b. A cut or slice made with an underarm stroke, as in tennis.

un·der·de·vel·oped (ŭn'dər-dĭ-vĕl'əpt) *adj.* 1. Not adequately or normally developed. 2. Not kept in a developing solution long enough to produce a normal degree of contrast <an *underdeveloped* photograph> 3. Having a low level of economic productivity and technological sophistication <*underdeveloped* countries>

un·der·do (ŭn'dər-dōō') *vt.* **-did** (-dĭd'), **-done** (-dŭn'), **-do·ing, -does** (-dŭz'). To do to an insufficient degree.

un·der·dog (ŭn'dər-dôg', -dŏg') *n.* 1. One expected to lose a contest or struggle, as in sports or politics. 2. One at a disadvantage, as because of discrimination.

un·der·done (ŭn'dər-dŭn') *adj.* Not sufficiently cooked.

un·der·draw·ers (ŭn'dər-drôrz') *pl.n.* Shorts or briefs worn as undergarments, esp. those for a man.

un·der·dress (ŭn'dər-drĕs') *n.* 1. Apparel worn beneath outer garments. 2. An outer garment worn under another as part of a costume or suit, as a dress beneath a tunic. —*vi.* (ŭn'dər-drĕs'). To dress too informally for the occasion. —**un'der·dressed'** *adj.*

un·der·drive (ŭn'dər-drīv') *n.* A gearing device causing the output drive shaft to rotate at a slower rate than the engine input shaft.

un·der·ed·u·cat·ed (ŭn'dər-ĕj'ə-kā'tĭd) *adj.* Poorly or insufficiently educated. —**un'der·ed'u·ca'tion** *n.*

un·der·em·pha·size (ŭn'dər-ĕm'fə-sīz') *vt.* **-sized, -siz·ing, -siz·es.** To fail to give enough emphasis to. —**un'der·em'pha·sis** (-sĭs) *n.*

un·der·em·ployed (ŭn'dər-ĕm-ploid') *adj.* Partially or inadequately employed, esp. employed at a low-paying job for which one is overqualified. —**un'der·em·ploy'ment** *n.*

un·der·es·ti·mate (ŭn'dər-ĕs'tə-māt') *vt.* **-mat·ed, -mat·ing, -mates.** To make too low an estimate of the quantity, degree, or worth of. —*n.* (ŭn'dər-ĕs'tə-mĭt). An estimate that is or proves to be too low. —**un'der·es'ti·ma'tion** *n.*

un·der·ex·pose (ŭn'dər-ĭk-spōz') *vt.* **-posed, -pos·ing, -pos·es.** To expose (film) to light for too short a time to produce normal image contrast. —**un'der·ex·po'sure** (-ĭk-spō'zhər) *n.*

un·der·feed (ŭn'dər-fēd') *vt.* **-fed** (-fĕd'), **-feed·ing, -feeds.** 1. To feed insufficiently. 2. To feed (an engine) with fuel from below.

un·der·flow (ŭn'dər-flō') *n. Computer Sci.* A data-processing error arising when a computed quantity is a smaller number than the device can represent.

un·der·foot (ŭn'dər-fo͝ot') *adv.* 1. Below or at one's feet <soft grass *underfoot*> 2. In the way <cats *underfoot* in the kitchen>

un·der·fund (ŭn'dər-fŭnd') *vt.* **-fund·ed, -fund·ing, -funds.** To provide insufficient funding for.

un·der·fur (ŭn'dər-fûr') *n.* The dense soft fur beneath the coarse outer hairs of certain mammals.

un·der·gar·ment (ŭn'dər-gär'mənt) *n.* A garment worn under outer garments, esp. one worn next to the skin.

un·der·gird (ŭn'dər-gûrd') *vt.* **-gird·ed** or **-girt** (-gûrt'), **-gird·ing, -girds.** To gird, support, or strengthen from beneath.

un·der·glaze (ŭn'dər-glāz') *n.* Coloring applied to pottery before it is glazed.

un·der·go (ŭn'dər-gō') *vt.* **-went** (-wĕnt'), **-gone** (-gôn', -gŏn'), **-go·ing, -goes** (-gōz') [ME *undergon* : *under,* under + *gon,* go.] 1. To be subjected to : EXPERIENCE. 2. To endure : suffer.

un·der·grad (ŭn'dər-grăd') *n.* & *adj. Informal.* Undergraduate.

un·der·grad·u·ate (ŭn'dər-grăj'o͞o-ĭt) *n.* A college or university student who has not yet received a degree. —*adj.* 1. Of, relating to, or characteristic of undergraduates. 2. Having undergraduate status.

un·der·ground (ŭn'dər-ground') *adj.* 1. Situated, occurring, or operating below the surface of the earth <*underground* chambers> <*underground* nuclear testing> 2. Conducted in secret : CLANDESTINE <*underground* resistance to a dictator> 3. Involved in secret or illegal activity <*underground* dealers in art> 4. Of or relating to an avant-garde movement or its films, publications, and art, usu. privately produced and of special appeal and often concerned with social or artistic experiment. —*n.* 1. A secret, often nationalist organization set up to resist or overthrow a government in power, such as an occupying military government. 2. *Chiefly Brit.* A subway system. 3. An avant-garde movement or publication. —*adv.* (ŭn'dər-ground'). 1. Below the surface of the earth. 2. In secret : STEALTHILY. —*vt.* **-ground·ed, -ground·ing, -grounds.** To situate under the ground, as telephone lines.

Underground Railroad *n.* A secret network operating in the United States before 1861 to help fugitive slaves reach sanctuary in the free states or Canada.

un·der·grown (ŭn'dər-grōn') *adj.* Not fully grown : PUNY.

un·der·growth (ŭn'dər-grōth') *n.* 1. a. Low plants, saplings, and shrubs growing beneath the trees in a forest. b. Something resembling this, as a dog's undercoat. 2. The state of being undergrown.

un·der·hand (ŭn'dər-hănd') *adj.* 1. Done in a treacherous or deceitful way : SNEAKY. 2. UNDERARM 2. —*adv.* 1. With an underhand movement. 2. Slyly : secretly.

un·der·hand·ed (ŭn'dər-hăn'dĭd) *adj.* 1. Underhand. 2. Lacking the required number of workers or players : SHORT-HANDED. —**un'der·hand'ed·ly** *adv.* —**un'der·hand'ed·ness** *n.*

un·der·hung (ŭn'dər-hŭng') *adj.* 1. a. Protruding from beneath <an *underhung* jaw> b. Supported by or lying over something that projects. 2. Resting on a supporting track, as a sliding door. 3. Underslung, as a vehicle.

un·der·kill (ŭn'dər-kĭl') *n.* Insufficient force to defeat an enemy.

un·der·laid (ŭn'dər-lād') *adj.* 1. Placed or laid underneath. 2. Supported or raised by something underneath : having an underlay.

un·der·lay (ŭn'dər-lā') *vt.* **-laid, -lay·ing, -lays.** 1. To put (one thing) under another. 2. To provide with a base or sublining. 3. To raise with an underlay in printing. —*n.* (ŭn'dər-lā'). 1. Something underlaid, as felt under a carpet. 2. Paper or other material inserted under type or cuts to raise the level of the printing bed.

un·der·let (ŭn'dər-lĕt') *vt.* **-let, -let·ting, -lets.** 1. To lease for less than the proper value. 2. To sublet.

un·der·lie (ŭn'dər-lī') *vt.* **-lay** (-lā'), **-lain** (-lān'), **-ly·ing, -lies.** 1. To be located under or below. 2. To be at the basis of <Many factors *underlie* inflation.> 3. To have a prior financial claim over <Dividends for preferred stock *underlie* those of common stock.>

un·der·line (ŭn'dər-līn', ŭn'dər-līn') *vt.* **-lined, -lin·ing, -lines.** 1. To draw a line under, esp. so as to emphasize. 2. To place emphasis on : STRESS. —*n.* (ŭn'dər-līn'). A line under something, as a symbol, word, or phrase, to indicate emphasis or italic type.

un·der·ling (ŭn'dər-lĭng) *n.* A subordinate or inferior.

un·der·lin·ing (ŭn'dər-lī'nĭng) *n.* 1. The act of drawing a line under. 2. Emphasis. 3. A lining for a garment.

un·der·lip (ŭn'dər-lĭp') *n.* The lower lip.

un·der·ly·ing (ŭn'dər-lī'ĭng) *adj.* 1. Lying under or beneath <*underlying* strata> 2. Basic : fundamental <an *underlying* truth> 3. Implicit : hidden <an *underlying* significance> 4. Taking precedence : PRIOR <an *underlying* financial claim>

un·der·manned (ŭn'dər-mănd') *adj.* Understaffed.

un·der·mine (ŭn'dər-mīn') *vt.* **-mined, -min·ing, -mines.** 1. To dig a mine or tunnel beneath. 2. To weaken by wearing away the supporting base <Water *undermined* the house's foundation.> 3. To weaken, injure, or impair, often by degrees <Poor eating habits *undermine* one's health.>

un·der·mod·u·late (ŭn'dər-mŏj'ə-lāt') *vt.* **-lat·ed, -lat·ing, -lates.** To utilize less of a sound reproduction or transmission device than optimally possible. —**un'der·mod'u·la'tion** *n.*

un·der·most (ŭn'dər-mōst') *adj.* & *adv.* Lowest in position, rank, or place.

un·der·neath (ŭn'dər-nēth') *adv.* [ME *underneth* < OE *underneoðan* : *under,* under + *neoðan,* below.] 1. In a place beneath : BELOW. 2. On the lower face or underside. —*prep.* 1. Under : below. 2. Under the power or control of. —*adj.* Lower : under. —*n.* The part or side below or under.

un·der·nour·ish (ŭn'dər-nûr'ĭsh) *vt.* **-ished, -ish·ing, -ish·es.** To provide with insufficient quantity or quality of nourishment to sustain proper health and growth. —**un'der·nour'ish·ment** *n.*

un·der·nu·tri·tion (ŭn'dər-no͞o-trĭsh'ən, -nyo͞o-) *n.* Inadequate nutrition due to undernourishment or poor assimilation of food.

un·der·pants (ŭn'dər-pănts') *pl.n.* Pants or briefs worn as underwear.

un·der·pass (ŭn'dər-păs') *n.* A passage underneath something, esp. a section of road that passes under a highway or railroad.

o͞o boot ou out th thin *th* this ŭ cut ûr urge y young yo͞o abuse zh vision ə about, item, edible, gallop, circus